REMARKS

Claims 16-29 were pending. In the Office Action dated November 24, 2004, the Examiner rejected claims 16-25 and 29 and objected to claims 26-28.

Applicants have herein added new claims 30-31; cancelled claims 21 and 23; and amended claim 22. Support for the amendments and new claims may be found throughout the specification, e.g., at page 16 (line 9) and page 17 (lines 6-8). No new matter has been added. Accordingly, claims 16-20, 22, and 24-31 are pending.

In light of the amendments and remarks herein, Applicants respectfully request reconsideration and allowance of all claims.

Objection to Claims 26-28

The Examiner objected to claims 26-28 under 37 CFR § 1.75(c) as being in improper form, stating that a multiple dependent claim cannot depend from any other multiple dependent claim. Applicants respectfully submit that claims 26-28 are not in improper form. Applicants note that the series of numbers in the claims refers to atom positions in the steroid hormone ligands, rather than to dependencies from particular claims. Applicants respectfully request withdrawal of these objections.

Rejections under 35 USC § 112, first paragraph

The Examiner rejected claim 23 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants have cancelled claim 23, rendering the rejection moot. Applicants respectfully request withdrawal of the rejection.

The Examiner also rejected claims 20 and 29 as being neither enabled nor described in the specification. While the Examiner agreed that the claims would have been enabled and adequately described if they were limited to the four named steroid hormone ligands, i.e.,

dexamethasone, 4-pregnen, 5α–androstan, and 4-androsten, the Examiner stated that "derivatives" of the four steroid hormone ligands were neither enabled nor described. More particularly, with respect to enablement, the Examiner stated that it would require undue experimentation to make and use the claimed derivatives, citing the various factors set forth in In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. With respect to written description, the Examiner stated that the genus of steroid hormone ligand "derivatives" was highly variant and that no common structural attributes identified members of the genus.

Applicants respectfully disagree and assert that the specification both enables and describes the recited method claims. Independent claims 16 and 17 are directed to methods for monitoring a binding interaction of a steroid hormone receptor (SHR) or a ligand binding domain (LBD) of a steroid hormone receptor, respectively, with a test ligand. The method includes:
(a) contacting a fluorescently-labeled steroid hormone ligand with a steroid hormone receptor (or a ligand binding domain (LBD) of a steroid hormone receptor) where the steroid hormone receptor is selected from the group consisting of an androgen receptor (AR), a glucocorticoid receptor (GR), and a progesterone receptor (PR), to form a reference mixture;
(b) measuring the fluorescence polarization of the reference mixture;
(c) contacting the reference mixture with the test ligand to form a test mixture;
(d) measuring the fluorescence polarization of the test mixture; and
(e) comparing the fluorescence polarization of the reference mixture to the fluorescence polarization of the test mixture to determine if the test ligand competes with the fluorescently-labeled steroid hormone ligand for binding to the steroid hormone receptor (or LBD of the steroid hormone receptor).

Thus, the claimed invention recites methods of using fluorescently-labeled steroid hormone ligands for evaluating test ligands, rather than steroid hormone ligands *per se*. The specification clearly enables and describes such methods. For example, with respect to enablement, the specification on page 16 describes a systematic, iterative approach to select steroid hormone ligands for use in the claimed methods. The approach can be used to evaluate the suitability of a variety of fluorescently-labeled steroid hormone ligands for use in the claimed

methods, including derivatives of the compounds recited in claims 20 and 29. In addition, by following the directed combinatorial approach using the core components listed in Table 1 at page 15, the specification provides adequate guidance to one having ordinary skill in the art to prepare a variety of steroid hormone ligands, including derivatives of the compounds recited in claims 20 and 29, that would be suitable for use in the claimed methods. Indeed, Applicants themselves used such an approach to obtain steroid hormone ligands that bind with high affinity and specificity to steroid hormone receptors; see page 17 describing ligands having a Kd of 0.8±0.1 nM for GR and a Kd of 2.5 nM for PR and the competitive binding data at Table 2, page 17 and Figure 3. Applicants respectfully assert that the claims are therefore enabled, as it would not require undue experimentation for a person of ordinary skill in the art to perform the recited methods.

With respect to written description of the "derivatives" of the four named steroid hormone ligands, Applicants also respectfully disagree. Contrary to the Examiner's assertion that "no common structural attributes" of the steroid hormone ligand genus were identified, the specification discloses core structures of four steroid hormone ligands (*i.e.*, dexamethasone, 4-pregnen, 5α–androstan, and 4-androsten). The specification indicates at Table 1 the particular positions on the steroid hormone rings of these core structures where derivatives could be made. Applicants respectfully note that numerous derivatives of these core structures at the recited positions had been made and were commercially available well before the filing date of the present application (see, for example, Sigma Chemical Catalog, 1994, at pages 116-120, 328, and 863-866, submitted herewith in an Information Disclosure Statement). Furthermore, on page 16, the specification describes a systematic, iterative approach to select steroid hormone ligand derivatives for use in the claimed methods. As one of ordinary skill in the art would have recognized, such an approach can be used with the four named steroid hormone ligands as well as their derivatives to select suitable steroid hormone ligands for use in the claimed methods. Accordingly, Applicants respectfully assert that that the specification provides adequate written description for the use of "derivatives" of the named steroid hormone ligands in the claimed methods.

Given all of the above, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejections under 35 USC § 112 second paragraph

The Examiner rejected claim 21 as being indefinite. Applicants have herein cancelled claim 21, thereby rendering the rejection moot. Applicants respectfully request withdrawal of the rejection.

Rejections under 35 USC § 103

The Examiner rejected claims 16-22 and 24-25 under 35 U.S.C. § 103 as being obvious over WO 99/27365 ("Lustig") in view of U.S. Patent No. 6,248,520 (hereinafter "the '520 patent"), and further in view of U.S. Patent No. 6,054,295 (hereinafter "the '295 patent"). In particular, the Examiner stated that Lustig teaches a fluorescence polarization method of screening for modulators of nuclear hormone receptor function comprising "measuring the binding of a sensor polypeptide . . . to a nuclear hormone receptor in the presence of a candidate agent. The sensor comprises a peptide with a receptor binding sequence and a fluorescent label." (emphasis added). While the Examiner acknowledged that Lustig does not teach a method where the receptor is AR, GR, or PR, or where the LBD is bound to GST, the Examiner asserted that the '520 patent disclosed the screening of antagonists of such receptors, and that the '295 patent disclosed fusion constructs of GST with LBD domains. In sum, the Examiner stated that it would have been obvious to one having ordinary skill in the art to modify the methods of Lustig to result in the claimed methods.

Applicants respectfully disagree. To avoid a hindsight-based obviousness analysis, there needs to be "a showing of the teaching or motivation to combine prior art references." In re Dembiczak, 175 F.3d 994 (Fed. Cir. 1999). Broad conclusory statements regarding the teaching of multiple references, standing alone, are not enough; particular findings regarding the locus of the suggestion, teaching, or motivation to combine prior art references are often required. Id. Moreover, suggestion itself is not enough: the suggested modification must have "a reasonable

expectation of success." Brown & Williamson Tobacco Corp. v. Philip Morris, Inc., 229 F.3d 1120 (Fed. Cir. 2000).

As indicated previously, independent claims 16 and 17 are directed to methods for monitoring a binding interaction of a steroid hormone receptor (SHR) or a ligand binding domain (LBD) of a steroid hormone receptor, respectively, with a test ligand. The method includes (a) contacting a fluorescently-labeled steroid hormone ligand with a steroid hormone receptor (or a ligand binding domain (LBD) of a steroid hormone receptor) where the steroid hormone receptor is selected from the group consisting of the androgen receptor (AR), the glucocorticoid receptor (GR), and the progesterone receptor (PR). As recognized by the Examiner, at no point does the Lustig reference teach or suggest a method for monitoring a binding interaction of a steroid hormone receptor (SHR) or a ligand binding domain (LBD) of a steroid hormone receptor where the steroid hormone receptor is selected from the group consisting of an androgen receptor (AR), a glucocorticoid receptor (GR), and a progesterone receptor (PR). Moreover, Lustig fails to teach the use of a fluorescently labeled steroid hormone ligand in his methods. Rather, all of the Lustig sensors include labeled peptides that bind as coactivators of the nuclear hormone receptors, and thus not as steroid hormone ligands, as required by the present claims.

The '295 and '520 patents do not cure the deficiencies of Lustig, either alone or in combination. The '295 patent discloses GST fusion constructs of full length nuclear hormone receptors and GST fusion constructs of nuclear hormone receptor ligand binding domains. The '520 patent discloses nucleic acid sequences for coactivator peptides and assays employing such coactivator peptides. At no point, however, does either patent teach or suggest that one having ordinary skill in the art should modify the methods of Lustig to use a fluorescently-labeled steroid hormone ligand, rather than a fluorescently-labeled coactivator peptide, to evaluate a test ligand, as required in the present claims. Furthermore, one having ordinary skill in the art would have had no reasonable expectation of success that the Lustig methods could be successfully modified to employ a fluorescently labeled steroid hormone ligand given the '520 and '295 disclosures. The simple fact that the '295 patent discloses GST fusion constructs of nNR1, nNR2, or nNR2-1 for expression purposes provides no reasonable expectation of success that

similar GST fusion constructs of AR, GR, or PR would function effectively in an FP assay for monitoring a binding interaction of a steroid hormone receptor (SHR) with a test ligand, as required by the present claims. Indeed, as one having ordinary skill in the art would recognize, ligand binding by a steroid hormone receptor can be greatly affected by numerous factors, including uncertain effects due to steric, charge, and conformational changes as a result of the addition of an N-terminal GST domain. Accordingly, the present claims are not obvious given Lustig in view of the '520 and '295 patents, and Applicants respectfully request withdrawal of the rejections.

CONCLUSION

Applicants submit that all claims are in condition for allowance, which action is requested. The Examiner is invited to telephone the undersigned attorney if such would expedite prosecution.

Enclosed is a $1810.00 check ($1020.00 for the Petition for Extension of Time Fee and $790.00 for the RCE fee). Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 5/24/05

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